USE OF COMPOUNDS HAVING THE BIOLOGICAL ACTIVITY OF VASOACTIVE INTESTINAL PEPTIDE FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

FIELD OF THE INVENTION

The present invention relates to peptides and pharmaceutical compositions comprising these peptides, that are highly biologically and pharmacologically active as therapeutic agents for the treatment of diseases related to chronic obstructive pulmonary disease (COPD) especially in medical interventions allowing for dilatation and inhibition of remodeling of bronchial tree. The peptides that can be used according to the invention for the treatment of said diseases comprise at least one specific highly conservative amino acid residue sequence that seems to play an important role in above-said diseases. It could be shown that especially the generally known naturally occurring peptides "vasoactive intestinal peptide (VIP)" and "pituitary adenylate cyclase-activating polypeptide (PACAP)", having these specific sequences, are potent drugs that can be successfully used for the treatment of COPD and related diseases which are preferably uncoupled from lung hypertension and are not pharmacologically correlated to pulmonary or arteriolar hypertension, respectively. Moreover, the invention relates to acute (adult) respiratory distress syndrome (ARDS) which can be successfully treated with the same peptide compounds as disclosed in case of COPD.

BACKGROUND OF THE INVENTION

Chronic obstructive pulmonary disease (COPD)

COPD is the overall term for a group of chronic conditions that are associated generally with the obstruction of lungs' airways. The disease may be accompanied by pulmonary hypertension (PPH, SPH) but not necessarily. The term COPD refers in more detail to the following disorders: chronic bronchitis, bronchiectasis and emphysema.

Chronic bronchitis is an inflammatory disease that begins in the smaller airways within the lungs and gradually advances to larger airways. It increases mucus production in the airways and increases the occurrence of bacterial infections in the bronchial tree, which, in turn, impedes airflow. This chronic inflammation induces thickening of the walls of the bronchial tree leading to increasing congestion in the lungs that results in dyspnoea. By definition, chronic bronchitis refers to a productive cough for at least three months of each of two successive years for which other causes have been ruled out.

Emphysema describes destruction of the lung architecture with enlargement of the airspaces and loss of alveolar surface area. Lung damage is caused by weakening and breaking the air sacs within the lungs. Several adjacent alveoli may rupture, forming one large space instead of many small ones. Larger spaces can combine into an even bigger cavity, called a bulla. As a result, natural elasticity of the lung tissue is lost, leading to overstretching and rupture. There is also less pull on the small bronchial tubes, which can cause them to collapse and obstruct airflow. Air that is not exhaled before the new inhale process gets trapped in the lungs, leading to shortage of breath. The sheer effort it takes to force air out of the lungs when exhaling can be exhausting.

Thus, the most common symptoms of COPD include shortness of breath, chronic coughing, chest tightness, greater effort to breathe, increased mucus production and frequent clearing of the throat. Patients are unable to perform their usual daily activities. Independent development of chronic bronchitis and emphysema is possible, but most people with COPD have a combination of the disorders. Both conditions decrease the lungs' ability to take in oxygen and remove carbon dioxide.

Long-term smoking is the most common cause of COPD, responsible for 80-90 percent of all cases. Other risk factors are heredity, second-hand smoke, air pollution, and a history of frequent childhood respiratory infections.

COPD is progressive and sometimes irreversible; there is currently no cure.
The clinical development of COPD is typically described in three stages, as defined by the American Thoracic Society:

Stage 1: Lung function (as measured by FEV1 or forced expiratory volume in one second) is greater than or equal to 50 percent of predicted normal lung function. There is minimal impact on health-related quality of life. Symptoms may progress during this stage, and patients may begin to experience severe breathlessness, requiring evaluation by a pulmonologist.

Stage 2: FEV1 lung function is 35 to 49 percent of predicted normal lung function, and there is a significant impact on health-related quality of life.

Stage 3: FEV1 lung function is less than 35 percent of predicted normal lung function, and there is a profound impact on health-related quality of life.

COPD prevalence increases with age, but there is a dramatic synergy with smoking such that smokers have higher COPD prevalence and mortality and lung function losses. A smoker is 10 times more likely than a non-smoker to die of COPD. When inhaled, the smoke paralyzes the microscopic hairs (cilia) lining the bronchial tree. Irritants and infectious agents caught in the mucus remain in the bronchial tree rather than being swept out by the cilia. This can inflame bronchial membranes, eventually resulting in chronic obstruction. Other indoor and outdoor air pollutants may damage the lungs and contribute to COPD.

According to the Annual World Health Report of the World Health Organisation (WHO), about 600 million people suffer from COPD worldwide, with some three million dying from the disease each year.

Although there is no cure for COPD, medications that are prescribed for people with COPD include:

- Fast-acting beta2-agonists, such as albuterol which can help to open narrowed airways;
- Anticholinergic bronchodilators, such as ipratropium bromide, and theophylline derivatives, all of which help to open narrowed airways;
- Long-acting bronchodilators, which help relieve constriction of the airways and help to prevent bronchospasm associated with COPD;
- Inhaled or oral corticosteroids, that help reduce inflammation;
- Antibiotics that are often given at the first sign of a respiratory infection to prevent further damage and infection in diseased lungs;
- Expectorants that help loosen and expel mucus secretions from the airways, and may help make breathing easier;
- Lung transplantation is being performed in increasing numbers and may be an option for people who suffer from severe emphysema;
- Lung volume reduction surgery, shows promise and is being performed with increasing frequency;
- Special treatments for AAT deficiency emphysema include AAT replacement therapy (a life-long process) are being evaluated;
- Current research into COPD is also focusing on gene therapy to substitute for the AAT deficiency.

Acute (adult) respiratory distress syndrome (ARDS)

ARDS is a life-threatening condition, a severe injury to most or all of both lungs. ARDS is the rapid onset of progressive malfunction of the lungs, especially with regard to the ability to take in oxygen, usually associated with the malfunction of other organs. The condition is associated with extensive lung inflammation and accumulation of fluid in the alveoli (air sacs) that leads to low oxygen levels in the lungs. ARDS is characterized by diffuse pulmonary microvascular injury resulting in increased permeability and, thus, non-cardiogenic pulmonary edema.

The definition of ARDS has changed over time. In the early 1960s Burke and coworkers utilized the term *High Output Respiratory Failure* to describe a type of respiratory failure characterized by the inability to provide adequate oxygenation and carbon dioxide excretion (Burke JF, Pontoppidan H, Welch CE: High output respiratory failure: An important cause of death ascribed to peritonitis or ileus. *Ann Surg* 1963;158:581-595). Ashbaugh and coworkers, in 1967, described a syndrome characterized by refractory hypoxemia, diffuse lung infiltrates on chest radiograph, and decreased lung compliance in a group of 12 patients suffering from severe respiratory failure (Ashbaugh DG, Bigelow DB, Petty TL, Levine BE: Acute respiratory distress in adults. *Lancet* 1967;2:319-323). In addition, these patients had different underlying diseases (e.g. pancreatitis, pneumonia, trauma). Originally, the authors named this condition the *Acute Respiratory Distress Syndrome of Adults.* However, in 1971 the same authors renamed the syndrome to what we now know as the *Adult Respiratory Distress Syndrome* or *Acute Respiratory Distress Syndrome* (ARDS) (Petty TL, Ashbaugh DG: The adult respiratory distress syndrome. Clinical features, factors influencing prognosis and principles of management. *Chest* 1971;60:233-239).

Terms frequently used when referring to this syndrome include: adult hyaline-membrane disease, adult respiratory insufficiency syndrome, congestive atelectasis, hemorrhagic lung syndrome, Da Nang lung, stiff-lung syndrome, shock lung, white lung and, wet lung among others (Taylor RW, Duncan CA: The adult respiratory distress syndrome. *Res Medica* 1983;1:17-21).

Although there are currently diverse opinions regarding the proper use of the term "ARDS", all definitions of this syndrome include patients who meet the following criteria (Dal Nogare AR: Adult respiratory distress syndrome. *Am J Med Sci* 1989;298(6):413-430; Murray JF, Matthay MA, Luce JM, Flick MR: An

expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis* 1988;138:720-723):

1) Clinical evidence of respiratory distress.

2) Chest radiograph revealing diffuse bilateral airspace disease ("pulmonary edema").

3) Hypoxemia that is difficult to correct with oxygen supplementation.

4) Hemodynamic evidence of a pulmonary artery occlusion (wedge) pressure < 18 mm Hg.

5) Thoracic static compliance less than 40 mL/cm of water.

The estimated incidence of ARDS in the USA in recent years has been calculated to be close to 150,000 new cases each year. The incidence is difficult to estimate because ARDS is often associated with other severe illnesses. But it is a common problem in hospital intensive care units. In a study by Fowler and coworkers, the incidence varied from 2% (e.g. in patients post coronary-artery bypass grafts or burns) to 36% (e.g. gastric bronchoaspiration) (Fowler AA, Hamman RF, Good JT, Benson K, Baird M, Eberly D, Petty T, Hyers T: Adult respiratory distress syndrome. Risk with common predisposition. *Ann Intern Med* 1983;98:593-597). In a similar cohort, Pepe *et. al.*, found that the incidence of ARDS ranged from 8% (in patients with multiple fractures) to 38% (in patients with sepsis) (Pepe PE, Potkin R, Holtman-Reus D, Hudson L, Carico J: Clinical predictors of the adult respiratory distress syndrome. *Am J Surg* 1982;144:124-128.

ARDS mortality varies based on the pre-existing health and age of the patient and the severity of the condition causing ARDS but remains high at 40-50 percent despite supportive therapy, including assisted respiration.

The major risk factors for the development of ARDS comprise:

- Severe, widespread infection (sepsis)
- Severe low blood pressure (shock)
- Pneumonia
- Aspiration (inhalation) of food into the lung
- Injury to the lungs from breathing high concentrations of oxygen
- Pulmonary embolism
- Chest injury
- Burns
- Overdose of a drug
- Disseminated intravascular coagulation

(Petty TL: Indicators of risk, course and prognosis in adult respiratory distress syndrome (ARDS). *Am Rev Resp Dis* 1985;132:471).

The basic abnormality in ARDS is the disruption of the normal alveolar-capillary barrier. Moreover, it is now evident that ARDS is not simply a form of pulmonary edema caused by increased microvascular permeability, but only a manifestation of a more generalized permeability defect (. Kreuzfelder E, Joka T, Keinecke HO, Obertacke V: Adult respiratory distress syndrome as a specific manifestation of a general permeability defect in trauma patients. *Am Rev Resp Dis* 1988;137:95-99). Research in recent years has been focused on possible mediators of lung injury in ARDS such as free radicals, proteinases and, soluble agents including cytokines, arachidonic acid metabolites and charged proteins.

The pathophysiologic consequences of lung edema in ARDS include a decrease in lung volumes, compliance, and large intrapulmonary shunts (blood perfusing unventilated segments of the lung). A fall in the residual volume is uniformly present and contributes to ventilation/perfusion inequality. The decrease in lung compliance is secondary to the increased lung recoil pressure of the edematous lung, which clinically increases the work of breathing and leads to respiratory muscle fatigue. The pulmonary vasculature is prominently affected in ARDS. Pulmonary hypertension not related to hypoxemia is a very common finding in patients with ARDS. Indeed, this is caused by a three-to-five fold increase in the pulmonary vascular resistance (PVR) and is associated with an increase in the right ventricular work (Zapol WM, Snider MR: Pulmonary hypertension in severe acute respiratory failure. *N Engl J Med* 1977;296:474-480). Pulmonary angiography studies performed within 48 hours of the onset of ARDS have shown that 48% of patients have demonstrable filling defects (intravascular thrombi) in vessels of more than 1 mm of diameter.

In most cases the diagnosis of ARDS is that of exclusion. Common symptoms include dyspnea, tachypnea, dry cough, retrosternal discomfort, and agitation. The patient appears in moderate to severe respiratory distress and may have cyanosis. Examination of the lungs may reveal coarse crackles and bronchial breath sounds. This clinical picture usually deteriorates, and the patient eventually requires assisted mechanical ventilation.

Barotrauma (e.g. pneumothorax, pneumomediastinum, subcutaneous emphysema) is a frequent complication in patients with ARDS managed with mechanical

ventilation. Patients at high risk for barotrauma, are those with very low lung compliance (e.g.< 20 cm of water). Development of barotrauma is most closely associated with alveolar distension, which best correlates with high peak inspiratory pressures.

ARDS has generally been characterized into three stages. In full-blown cases, these three stages unfold sequentially over a period of several weeks to several months.

Exudative stage: Characterized by accumulation in the alveoli of excessive fluid, protein and inflammatory cells that have entered the air spaces from the alveolar capillaries. The exudative phase unfolds over the first 2 to 4 days after onset of lung injury.

Fibroproliferative stage: Connective tissue and other structural elements in the lungs proliferate in response to the initial injury. Under a microscope, lung tissue appears densely cellular. Also, at this stage, there is a danger of pneumonia sepsis and rupture of the lungs causing leakage of air into surrounding areas.

Resolution and Recovery: During this stage, the lung reorganizes and recovers. Lung function may continue to improve for as long as 6-12 months and sometimes longer, depending on the precipitating condition and severity of the injury. It is important to remember that there may be and often are different levels of pulmonary recovery amongst individuals who suffer from ARDS.

People with acute respiratory distress syndrome are treated in an intensive care unit. Oxygen therapy is vital to correct low oxygen levels. Treatment for ARDS consists of mechanical ventilation along with fluid removal and a supportive breathing technique called positive end expiratory pressure (PEEP). The goal of mechanical ventilation is to support the patient's breathing during the time needed for the patient's lungs to heal.

To date, there are no specific pharmacological interventions of proven value for the treatment of ARDS. Although corticosteroids and prostaglandin E1 have been widely used clinically, studies have failed to show any benefit in outcome, lung compliance, pulmonary shunts, chest radiograph, severity score or survival (Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF: Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Am Rev Respir Dis* 1988;138:62-68; Bernard GR, Luce J, Sprung C, Reinaldo J, Tate R, Sibblad W, Kariman K, Higgins S, Bradley R, Metz C, Harris T, Brigham K: High-dose corticosteroids in patients with the adult respiratory distress syndrome. *N Engl J*

Med 1987;317:1565-1570; Melot C, Leujeune P, Leemam M, Moraine JJ, Neaije R: Prostaglandin E1 in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1989;139:106-110).

A number of new approaches are being explored in ARDS, especially addressing inhibitors of tumor-necrosis-factor alpha (TNF-α) and phosphodiesterase inhibitors. No measures are presently known to prevent ARDS.

VIP and PACAP

VIP and PACAP are human peptides synthesized in various components of the central nervous system, e.g. specific brain regions like hippocampus and cortex as well as in the pituitary gland and peripheral ganglia. VIP is furthermore secreted by immune cells and by some neoplastic cells (e.g. pancreatic cancer).

Vasoactive intestinal peptide (VIP):

VIP is a 28 amino acid peptide consisting of the following amino acid sequence (from N- to C-terminal):

His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn.

Healthy individuals exhibit low concentration of VIP (<40 pg/ml serum).

VIP is a widely distributed peptide hormone that mediates a variety of physiological responses including gastrointestinal secretion, relaxation of gastrointestinal vascular and respiratory smooth muscle, lipolysis in adipocytes, pituitary hormone secretion, and excitation and hyperthermia after injection into the central nervous system. Under physiologic conditions VIP acts as a neuroendocrine mediator. Some recent findings suggest that VIP also regulates growth and proliferation of normal as well as malignant cells (*Hultgardh, Nilsson A., Nilsson, J., Jonzon, B. et al. Growth-inhibitory properties of vasoactive intestinal polypeptide. Regul.Pept. 22, 267-274. 1988*). Importantly, VIP is a potent anti-inflammatory agent, as treatment with VIP significantly reduced incidence and severity of arthritis in an experimental model, completely abrogating joint swelling and destruction of artilage and bone *(Delgado et al. Vasoactive intestinal peptide prevents experimental arthritis by downregulating both autoimmune and inflammatory components of the disease. Nature Med. 7, 563-568, 2001).* The biological effects are mediated via specific receptors (VIP-R) located on the surface membrane of various cells (*Ishihara, T.,*

Shigemoto, R., Mori, K. et al. Functional expression and tissue distribution of a novel receptor for vasoactive intestinal polypeptide. Neuron 8, 811-819. 1992).VIP may exert stimulating and trophic effects on neoplastic cells from neuroblastoma, breast, lung and colon cancer (*e.g. Moody et al., Proc. Natl. Acad. Sci. USA, 90, 4345, 1993*), inducing its own receptors by feedback mechanisms. In some cases VIP produced dose-dependent stimulation of mitosis (*Wollman et al., Brain Res., 624, 339, 1993*). VIP and biologically functional analogues and derivatives thereof are shown to have vascular smooth muscle relaxant activity (*Maruno, K., Absood, A., and Said, S. I. VIP inhibits basal and histamine-stimulated proliferation of human airway smooth muscle cells. Am.J.Physiol. 268, L1047-L1051, 1995*), hair growth activity, apoptosis activity enhanced sustained bronchodilation activity without remarkable cardiovascular side effects, and are effective against disorders or diseases relating to bronchial spasms including asthma, some cases of hypertension, impotence, ischaemia, dry eye and mental disorders, such as Alzheimer's disease (see e.g. *WO 9106565, EP 0536741, US 3,880,826, EP 0204447, EP 0405242, WO 9527496, EP 0463450, EP 0613904, EP 0663406, WO 9735561, EP 0620008*).

VIP receptor has been detected on airway epithelium of the trachea and the bronchioles. It is also expressed in macrophages surrounding capillaries, in connective tissue of trachea and bronchi, in alveolar walls, and in the subintima of pulmonary veins and pulmonary arteries. Pepidergic nerve fibers are considered the source of VIP in the lungs (e.g.: *Dey, R. D., Shannon-WA, Jr, and Said, S. I. Localization of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cat, and human subjects. Cell and Tissue Research 220, 231-238. 1981; Said, S. I. Vasoactive intestinal polypeptide (VIP) in asthma. Ann.N.Y.Acad.Sci. 629, 305-318. 1991*). VIP decreases the resistance in the pulmonary vascular system (e.g.: *Hamasaki, Y., Mojarad, M., and Said, S. I. Relaxant action of VIP on cat pulmonary artery: comparison with acetylcholine, isoproterenol, and PGE1. J.Appl.Physiol. 54, 1607-1611. 1983; Iwabuchi, S., Ono, S., Tanita, T. et al. Vasoactive intestinal peptide causes nitric oxide-dependent pulmonary vasodilation in isolated rat lung. Respiration 64, 54-58. 1997; Saga, T. and Said, S. I. Vasoactive intestinal peptide relaxes isolated strips of human bronchus, pulmonary artery, and lung parenchyma. Trans.*Assoc.Am.Physicians. *97, 304-310. 1984).* Further studies show a high rate of VIP-R expression in the lung which is reflected in a high uptake of radiolabeled VIP in the lung of PPH patients who were injected 99mTc-VIP (e.g.: *Raderer, M., Kurtaran, A., Hejna, M. et al. 123I-labelled vasoactive intestinal peptide*

receptor scintigraphy in patients with colorectal cancer. Br.J.Cancer 78, 1-5. 1998; Raderer, M., Kurtaran, A., Yang, Q. et al. Iodine-123-vasoactive intestinal peptide receptor scanning in patients with pancreatic cancer. J.Nucl.Med. 39, 1570-1575. 1998; Raderer, M., Kurtaran, A., Leimer, M. et al. Value of peptide receptor scintigraphy using (123)I-vasoactive intestinal peptide and (111)In-DTPA-D-Phe1-octreotide in 194 carcinoid patients: Vienna University Experience, 1993 to 1998. J.Clin.Oncol. 18, 1331-1336. 2000; Virgolini, I., Kurtaran, A., Raderer, M. et al. Vasoactive intestinal peptide receptor scintigraphy. J.Nucl.Med. 36, 1732-1739. 1995). Moreover, VIP and the compounds as disclosed above and below were recently shown by the inventors of the present application to be effective in the treatment of PPH, SPH and arteriolar hypertension (PCT/EP01/13590).

Pituitary adenylate cyclase-activating polypeptide (PACAP):

PACAP is a neuropeptide isolated from the ovine hypothalamus consisting of the following 38 amino acid residues containing sequence (from N- to C-terminal):
His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-Gly-Lys-Arg-Tyr-Lys-Gln-Arg-Val-Lys-Asn-Lys.

Two forms of the peptide have been identified: PACAP-38 and the C-terminally truncated PACAP-27. PACAP-27 that shares 68 percent homology with VIP has the following sequence (from N- to C-terminal):
His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu.

PACAP is very potent in stimulating adenylate cyclase and thus increasing adenosine 3, 5 -cyclic monophosphate (cAMP) in various cells. The compound functions as a hypothalamic hormone, neurotransmitter, neuromodulator, vasodilator, and neurotrophic factor. The major regulatory role of PACAP in pituitary cells appears to be the regulation of gene expression of pituitary hormones and/or regulatory proteins that control growth and differentiation of the pituitary glandular cells. These effects appear to be exhibited directly and indirectly through a paracrine or autocrine action. PACAP plays an important role in the endocrine system as a potent secretagogue for adrenaline from the adrenal medulla. The compound also stimulates the release of insulin. The stage-specific expression of PACAP in testicular germ cells during spermatogenesis suggests its regulatory role in the maturation of germ cells. In the ovary, PACAP is transiently

expressed in the granulosa cells of the preovulatory follicles and appears to be involved in the LH-induced cellular events in the ovary, including prevention of follicular apoptosis. In the central nervous system, PACAP acts as a neurotransmitter or a neuromodulator. More important, PACAP is a neurotrophic factor that may play a significant role during the development of the brain. In the adult brain, PACAP appears to function as a neuroprotective factor that attenuates the neuronal damage resulting from various insults. PACAP is widely distributed in the brain and peripheral organs, notably in the endocrine pancreas, gonads, and respiratory and urogenital tracts. Two types of PACAP binding sites have been characterized. Type I binding sites exhibit a high affinity for PACAP (and a much lower affinity for VIP), whereas type II binding sites have similar affinity for PACAP and VIP. Molecular cloning of PACAP receptors has shown the existence of three distinct receptor subtypes. These are the PACAP-specific PAC1 receptor, which is coupled to several transduction systems, and the two PACAP/VIP-indifferent VPAC1 and VPAC2 receptors, which are primarily coupled to adenylyl cyclase. PAC1 receptors are particularly abundant in the brain and pituitary and adrenal glands whereas VPAC receptors are expressed mainly in the lung, liver, and testes.

SUMMARY OF THE INVENTION

It is object of the present invention to provide novel use of compounds, which are useful for the prevention and/or treatment of COPD and related diseases, and methods wherein said compounds are used.

Surprisingly it was found that peptides or polypeptides comprising the highly conservative decapeptide sequence

Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu

show highly efficacy when administered to patients suffering from COPD, ARDS which are preferably uncoupled from pulmonary hypertension, and related diseases such as unspecific chronic and / or irritating coughing, or symptoms which can be related to said diseases or malfunctions. It could be shown by the inventors of this invention that said compounds and especially the peptides more specified below are active in COPD and ARDS, preferably chronic bronchitis, bronchiectasis and emphysema. Surprisingly, said compounds are highly active in patients suffering from COPD which is preferably not accompanied by lung hypertension, such as primary or secondary pulmonary hypertension (PPH, SPH). The peptides described in this specification are furthermore suitable for the prophylaxis and treatment of smoker's cough and similar symptoms. Moreover, it could be shown that treating of patients with said peptides improves

distinctly all concomitant symptoms as described above, and the general state of health of patients suffering from COPD, preferably chronic bronchitis, emphysema, chronic cough, chronic irritating cough, smoker's cough and so on.

The forced expiratory volume (FEV) and the partial pressure of arterial oxygen (paO2) can be increased dramatically in COPD patients treated, for example, with VIP to 10 – 50 % within 2 – 5 months. In more detail, the percentage increase of FEV1 varies between 20 and 30 % after approximately 3 months, whereas the increase of paO2 varies between 30 – 50% under the same conditions.

It was reported earlier by other authors (see Background of the Invention) that VIP is considered as effective in the treatment of asthma. The results of the present investigation show that VIP and the related compounds as defined in this invention have distinctly more efficacy in the treatment of COPD than in asthma. Interestingly, in all these cases the above-mentioned peptides do not primarily act on COPD like typical bronchodilatory drugs or anti-inflammatory drugs such as corticosteroids as mentioned below but have obviously a different influence on pathologic bronchial tissue. Thus, VIP and related compounds are not only an alternative for generally known and used drugs in this field, but provide an additional pharmacological efficacy profile.

It is a further object of the invention to provide novel and highly efficacious use of the same compounds as described in context with COPD for the treatment of another lung failure which is acute (adult) respiratory distress syndrome (ARDS), the symptoms of which are listed above.

Compounds comprising above-cited decapeptide sequence and having totally 10 – 60, preferably 10 – 38, more preferably 10 – 28 or 10 – 23 amino acid residues have very similar or identical biological function as VIP or PACAP which also comprise said highly conservative sequence. It is another result of the present invention that VIP, PACAP and also its truncated forms, for example PACAP-27, are also highly active compounds for the prophylaxis and treatment of COPD by inhibition and/or regulation of cellular processes underlying the said diseases in humans.

Generally, it was found that VIP- and PACAP-like peptides and polypeptides can show the above-described therapeutic function and efficacy which have the following amino acid sequence:

$(A)_n$- Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-$(B)_m$

wherein A, B is any natural occurring amino acid residue, A and B are independently from each other; and n, m is an integer having values from 0 – 25; n and m being independently from each other. The value of m is preferably 4 – 18, more preferably 5 – 15, and most preferably 10 – 15.

Polypeptides or peptides, wherein $(A)_n$ (if n > 2) comprises the tripeptide sequences His-Ser-Asp and /or Phe-Thr-Asp in N-terminal direction near by (1 – 10 amino acid residues) above-specified decapeptide sequence have an enhanced activity.

Thus polypeptides, wherein

$(A)_n$ (if n > 2) has the meaning of $(X)_o$-Phe-Thr-Asp-$(Y)_p$ and

$(X)_o$ (if o > 2) has the meaning of $(X')_q$-His-Ser-Asp-$(X'')_r$

wherein X, Y, X', X" is any natural occurring amino acid residue; and o, p, is an integer having values from 0 – 11, and r, q is an integer having values from 0 – 4, show especially improved efficacy . Preferred values of o and p are 0 – 8, more preferably 1 – 5. Preferred values of r are 0 – 2.

Preferred examples falling under the generic formula are:

His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn (VIP);

His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-Gly-Lys-Arg-Tyr-Lys-Gln-Arg-Val-Lys-Asn-Lys (PACAP-38)

His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu (PACAP-27);

This invention includes also compounds falling under the above-specified formula: $(A)_n$-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-$(B)_m$

wherein A, B is any natural occurring amino acid residue, A and B are independently from each other; and n, m is an integer having values from 0 – 25, n and m being independently from each other, provided that VIP, PACAP and PACAP-27 (truncated PACAP) is excluded.

Preferred examples of these novel polypeptides are:

(i) Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

(ii) Phe-Thr-Asp-X^1-X^2-X^3-X^4-X^5-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn

(iii) Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn;

(iv) Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

(v) His-Ser-Asp-X^1-X^2-Phe-Thr-Asp-X^3-X^4-X^5-X^6-X^7-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

(vi) His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu,

(vi) His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

(vii) His-Ser-Asp-X^1-X^2-Phe-Thr-Asp-X^3-X^4-X^5-X^6-X^7-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-X^8-X^9-X^{10}-X^{11}(-X^{12});

(viii) His-Ser-Asp-X^1-X^2-Phe-Thr-Asp-X^3-X^4-X^5-X^6-X^7-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-X^{19}-X^{20}-X^{21}-X^{22};

wherein $X^1 - X^{22}$ is any naturally occurring amino acid residue.

In summary, it is an object of this invention to provide the following topics:

- A use of a compound for the manufacture of a medicament for the treatment of a patient suffering from chronic obstructive pulmonary disease (COPD), which is functionally uncoupled from or pharmacologically not correlated to hypertension diseases, wherein said compound is a peptide or a polypeptide comprising the following amino acid sequence:

  Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu.

- A said use, wherein said peptide or a polypeptide further comprises at least one of the following amino acid sequences:

  His-Ser-Asp; Phe-Thr-Asp.

- A said use, wherein said peptide or a polypeptide further comprises the amino acid sequences His-Ser-Asp and Phe-Thr-Asp.

- A said use, wherein said peptide or a polypeptide has the following amino acid sequence:

$(A)_n$- Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-$(B)_m$

wherein A, B is any natural occurring amino acid residue, A and B are independently from each other; and n, m is an integer having values from 0 – 25; n and m being independently from each other.

- A said use, wherein, if n > 2, $(A)_n$ has the following sequence:

  $(X)_o$-Phe-Thr-Asp-$(Y)_p$

  wherein X, Y is any natural occurring amino acid residue, X and Y are independently from each other; and o, p is an integer having values from 0 – 11, o and p being independently from each other.

- A said use, wherein, if o > 2 $(X)_o$ has the following sequence:

  $(X')_q$-His-Ser-Asp-$(X'')_r$

  wherein X', X" is any natural occurring amino acid residue, X' and X" are independently from each other; and r, q is an integer having values from 0 – 4, r and q being independently from each other.

- A said use, wherein the sequence of said peptide or polypeptide is selected from the following group:

  (i) Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

  (ii) Phe-Thr-Asp-X^1-X^2-X^3-X^4-X^5-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn

  (iii) Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn;

  (iv) Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

  (v) His-Ser-Asp-X^1-X^2-Phe-Thr-Asp-X^3-X^4-X^5-X^6-X^7-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

  (vi) His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu,

  (vi) His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu;

  (vii) His-Ser-Asp-X^1-X^2-Phe-Thr-Asp-X^3-X^4-X^5-X^6-X^7-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-X^8-X^9-X^{10}-X^{11}(-X^{12});

  (viii) His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn (VIP);

(ix) His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu (PACAP-27);

(x) His-Ser-Asp-X^1-X^2-Phe-Thr-Asp-X^3-X^4-X^5-X^6-X^7-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-X^8-X^9-X^{10}-X^{11}-X^{12}-X^{13}-X^{14}-X^{15}-X^{16}-X^{17}-X^{18}-X^{19}-X^{20}-X^{21}-X^{22};

(xi) His-Ser-Asp-Gly-Ile-Phe-Thr-Asp-Ser-Tyr-Ser-Arg-Tyr-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Ala-Ala-Val-Leu-Gly-Lys-Arg-Tyr-Lys-Gln-Arg-Val-Lys-Asn-Lys (PACAP-38);

wherein $X^1 - X^{22}$ is any naturally occurring amino acid residue.

- A said use, wherein said peptide or polypeptide is brought in a stabilized form.
- A said use, wherein said peptide is pegylated.
- A said use, wherein the COPD is selected from the following group: chronic bronchitis, pulmonary emphysema, chronic cough.
- A said use, wherein a daily administration of the medicament leads to an improvement of the FEV1 value of more than 15% after 3 months.
- A said use, wherein a daily administration of the medicament leads to an improvement of the paO2 value of more than 35% after 3 months.
- A use of a peptide or polypeptide as defined in any of the relevant claims for the manufacture of a medicament for the improvement or recovery of the general state of health which had been reduced by chronic bronchitis and chronic cough.
- A use of a compound for the manufacture of a medicament for the treatment of a patient suffering from acute (adult) respiratory distress syndrome (ARDS), wherein said compound is a peptide or a polypeptide as defined in any of the relevant claims.
- A method for treatment of COPD comprising administering to a patient a peptide or a polypeptide as defined in any of the relevant claims.
- A said method, wherein the COPD is selected from the group: chronic bronchitis, pulmonary emphysema, chronic cough.
- A said method, wherein a daily administration of the peptide or polypeptide leads to an improvement of the FEV1 value of more than 15% after 3 months.
- A said method, wherein a daily administration of the peptide or polypeptide leads to an improvement of the paO2 value of more than 35% after 3 months.

- A method for treatment of ARDS comprising administering to a patient a peptide or a polypeptide as defined in any of the relevant claims.
- A said method comprising inhalation of an aerosol of the peptide or polypeptide by the patient.
- A said method, wherein the aerosol is made from a isotonic NaCl solution containing said peptide or polypeptide, preferably in a pegylated form.
- A pharmaceutical composition consisting of a aqueous sodium chloride solution in an isotonic concentration comprising VIP, PACAP or another peptide as defined in any of the relevant in a pegylated form.
- A said pharmaceutical composition, wherein said peptide or polypeptide is present in a concentration range between 3 and 300 mg / L.
- A said pharmaceutical composition as aerosol.

DETAILED DESCRIPTION

Suitable compounds which have the therapeutic effect according to the invention, are compounds which have the same, but also reduced or enhanced, biological activity of VIP or PACAP. Preferred compounds according to the invention have the same or an enhanced biological activity. All compounds falling under this group comprise the sequence Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu.

The invention includes also derivatives of the disclosed peptides and polypeptides having the same biological activity.

The term "**same biological activity**" means the biological, physiological or therapeutic activity or functionality compared with the relevant properties of said peptides and polypeptides, preferably VIP or PACAP.

The term "**derivative**" means a peptide compound which is derived more or less directly from the corresponding peptide, such as VIP or PACAP as such, and is altered by some additions, deletions, mutations or modifications without altering the biological properties of the parent peptide. Suitable VIP derivatives are, for example, disclosed in WO 8905857, WO 9106565, EP 0663406 and WO 9729126 (Fmoc protected VIP). The term includes also conjugates of peptides and polypeptides according to the invention that consist of the parent peptide or polypeptide coupled to lipophilic entities, such as liposomes. VIP – liposome products are, for example, disclosed in WO 9527496 or WO

9735561, and have improved properties with respect to bioavailability and proteolytic degradation. Furthermore, the term includes also fragments, slightly modified fragments including truncated forms.

The term "**analogue**" means a compound which may have a different structure and composition compared with the polypeptides and peptides according to the invention, preferably VIP, however without having altered biological properties. VIP analogues may be natural or synthetic peptides but also non-peptides. Preferably, VIP analogues according to the invention are peptides. Examples for known VIP analogues are disclosed in EP 0325044 (cyclic peptides), EP 0225020 (linear peptides), EP 0536741 (cyclic VIP modifications), EP 0405242, EP 0184309 and EP 0613904. The term includes also VIP or PACAP homologues, which are not VIP or PACAP but show great structural similarity to VIP. Such a VIP homologue according to the invention is PACAP itself and its truncated form PACAP-27. The term also includes such homologues that could form, like VIP, amphipathic helices. Preferred VIP / PACAP homologues are peptides that comprise one or more consensus sequences. Examples are peptide histidine isoleucine (PHI), peptide histidine methionine (PHM), human growth hormone releasing factor (GRF), pituitary adenylate cyclase activating peptide (PACAP), secretin and glucagon.

The term "**stabilized form**" means a derivative or analogue wherein the parent peptide was altered in order get more stability and increased half-life in blood and serum. Such stabilized forms are preferred if the polypeptide is fragmented by enzyme activity. Possible stabilized forms are cyclic peptides or polypeptides like cyclic VIP or cyclic PACAP, fusion proteins, preferably Fc-fusion proteins or pegylated polypeptides, for example pegylated VIP or PACAP. Methods for manufacturing such polypeptides are well known in the art. Polypeptides and proteins may be protected against proteolysis by the attachment of chemical moieties. Such attachment may effectively block the proteolytic enzyme from physical contact with the protein backbone itself, and thus prevent degradation. Polyethylene glycol is one such chemical moiety that has been shown to protect against proteolysis (Sada, et al., J. Fermentation Bioengineering 71: 137-139, 1991). In addition to protection against proteolytic cleavage, chemical modification of biologically active proteins has been found to provide additional advantages under certain circumstances, such as increasing the stability and circulation time of the therapeutic protein and decreasing immunogenicity. (US. 4,179,337; Abuchowski et al.,

Enzymes as Drugs.; J.S. Holcerberg and J. Roberts, eds. pp. 367-383, 1981; Francis, *Focus on Growth Factors* 3: 4-10; EP 0 401 384). The addition of polyethylene glycol increases stability of the peptides and polypeptides of this invention at physiological pH as compared to non-pegylated compounds. The pegylated polypeptide /protein is also stabilized with regard to salts.

The term "**fusion protein**" means a compound, especially a stabilized form, consisting of a polypeptide according to the invention, preferably VIP or a VIP derivative or analogue, such as PACAP, which is fused to another peptide or protein. Such a protein is preferably an immunglobulin molecule, more preferably a fragment thereof, most preferably a Fc portion of an IgG molecule, preferably an IgG1. A Fc-VIP fusion protein is described in WO 200024278 and shows an improved half-life in serum and blood. A further example is Fc-PACAP and FC-PACAP-27.

The compound according to the invention can be used as medicament or as diagnostic means to evaluate pathological conditions in an individual.
The term "**individual**" preferably refers to mammals, especially humans. The compound is used in a pharmaceutical composition and formulations, comprising, as a rule, a pharmaceutically acceptable carrier, excipient or diluents. Techniques for the formulation and administration of the compounds of the present invention may be found in "Remington's Pharmaceutical Sciences" Mack Publishing Co., Easton PA

As used herein, the term "**pharmaceutically acceptable carrier**" means an inert, non toxic solid or liquid filler, diluent or encapsulating material, not reacting adversely with the active compound or with the patient, or any other formulation such as tablets, pills, dragees, capsules, gels, syrups, slurries, suspensions and the like. Suitable, preferably liquid carriers are well known in the art such as sterile water, saline, aqueous dextrose, sugar solutions, ethanol, glycols and oils, including those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil and mineral oil.
The formulations according to the invention may be administered as unit doses containing conventional non-toxic pharmaceutically acceptable carriers, diluents, adjuvants and vehicles that are typical for parenteral administration.

The term "**parenteral**" includes herein subcutaneous, intravenous, intra-articular and intratracheal injection and infusion techniques. Parenteral compositions and combinations are most preferably administered intravenously either in a bolus form or as a constant fusion according to known procedures.

Tablets and capsules for oral administration contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, and wetting agents. The tablets may be coated according to methods well known in the art.

Unit doses according to the invention may contain daily required amounts of the compound according to the invention, or sub-multiples thereof to make up the desired dose. The optimum therapeutically acceptable dosage and dose rate for a given patient (mammals, including humans) depends on a variety of factors, such as the activity of the specific active material employed, the age, body weight, general health, sex, diet, time and route of administration, rate of clearance, enzyme activity, the object of the treatment, i. e., therapy or prophylaxis and the nature of the disease to be treated. Therefore, in compositions and combinations in a treated patient (in vivo) a pharmaceutical effective daily dose of the compound of this invention is between about 5 ng and 200 µg /kg body weight, preferably between 20 ng and 20 µg /kg body weight.

The preferred administration of the peptides according to this invention is the inhalation of aqueous solutions containing a preferably water-soluble peptide having the biological and pharmacological activity of VIP, PACAP and related analogues, variants, derivatives and so on, as described above. The aqueous solution is preferably an isotonic saline solution (NaCl) which can contain additional drugs or other suitable incredients. Preferably, the peptide compounds are used in said solutions in a stabilized form as specified above. Especially preferred solutions are istonic NaCl solutions containing the peptide in a pegylated form. The concentration of the peptide used in therapy in said solutions vary according to the invention between 10 mg and 300 mg / L solution, preferably between 30 mg and 100 mg / L. If stabilized forms, such as pegylated VIP or pegylated PACAP, are used the concentration as well as the over-all dosage of the selected peptide of the invention can decreased, as a rule. The inhalation of the peptides or polypeptides according to the invention can be carried out, as a rule, 1 – 4 times a day for 5 – 45 minutes, preferably 10 – 20 minutes, according to the severity of the disease and the efficacy of the compounds used for the treatment.

For inhalations the compound according to the invention is preferably brought in an aerosol form. Aerosols and techniques to make them are well known in the art. Aerosols applicable by inhalers containing a peptide or polypeptide of the invention, for example, VIP or PACAP are preferred in the case of COPD. Administration by nasal spray techniques are also suitable.

Combination therapy

The compounds of the invention may be administered to a subject in need thereof, e.g. a human patient, by itself or in pharmaceutical compositions where they are mixed with suitable carriers or excepients at doses that are sufficient for at least the inhibition of the diseases' progression. Therapeutically effective doses may be administered alone or as adjunctive therapy in combination with other pharmaceutically effective compounds, such as compounds with other drugs, e.g. fast-acting beta2-agonists (such as albuterol), anticholinergic bronchodilators (such as ipratropium bromide), long-acting bronchodilators, inhaled or oral corticosteroids, antibiotics, or antiproliferative compounds, e.g. D-24851, Imatinib mesylate, guanylhydrazone CNI-1493. This invention also relates to the combination of the compounds described in the present invention with at least one of the abovementioned drugs.

It is likely that the therapy with the compounds of the invention, alone or in combination with the abovementioned substances may lower existing but undesired drug effects in a subject in need of those drugs.

Surprisingly, it was found that the peptides and polypeptides as defined above and in the claims, above all VIP and PACAP, have beneficial effects in the treatment of ARDS and COPD as demonstrated in the following examples. These data show a dramatic improvement for the treatment of as yet not sufficiently treatable diseases. It is a benefit of this invention that all tested polypetides comprising the highly conservative decapeptide sequence as depicted in above are efficacious.

SHORT DESCRIPTION OF THE FIGURES:

Fig. 1: Figure 1 depicts the forced expiratory volume in one second (FEV1) (1a) and the partial pressure of arterial oxygen (1b) of a first patient treated with VIP.

Fig. 2: Figure 2 depicts the forced expiratory volume in one second (FEV1) (1a) and the partial pressure of arterial oxygen (1b) of a second patient treated with VIP.

Fig. 3: Figure 3 depicts the partial pressure of arterial oxygen (PaO2), the partial pressure of arterial carbon dioxide (PaCO2), and the arterial-alveolar oxygen difference (AaDO2) of a third patient treated with VIP.

Fig. 4: Figure 4 depicts the vital capacity (VC), the forced expiratory volume in one second (FEV1), the total lung capacity (TLC), and the remaining volume (RV) of a third patient treated with VIP.

Fig. 5: Figure 5 depicts the arterial-alveolar oxygen difference (AaDO2) of a fourth, fifth, and sixth patient with severe ARDS treated with VIP.

Fig. 6: Figure 6 depicts the Horowitz Index of a fourth, fifth, and sixth patient with severe ARDS treated with VIP.

Fig. 7: Figure 7 depicts the measure for oxygen capacity of hemoglobin (FiO2) of a fourth, fifth, and sixth patient with severe ARDS treated with VIP.

Fig. 8: Figure 8 depicts the mean pulmonary artery pressure (mPAP) of a fourth, fifth, and sixth patient with severe ARDS treated with VIP.

Fig. 9: Figure 9 depicts the pulmonary vascular resistance (PVR) of a fourth, fifth, and sixth patient with severe ARDS treated with VIP.

Fig. 10: Figure 10 depicts the mean arterial blood pressure (mABP) of a fourth, fifth, and sixth patient with severe ARDS treated with VIP.

Fig. 11: Figure 11 depicts the intrapulmonal shunt of a fifth patient with severe ARDS treated with VIP (timeframe of 24 hours).

Fig. 12: Figure 12 depicts the intrapulmonal shunt of a fifth patient with severe ARDS treated with VIP (timeframe of 20 minutes).

EXAMPLES

Patient 1:

A patient with severe COPD but no realizable lung hypertension symptoms inhaled VIP (100 µg in 3 ml NaCl 0,9%) for 15 minutes via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Lung function parameters FEV1 (forced expiratory volume in one second) and PaO_2 (Partial pressure of arterial oxygen) were measured.

FEV1 (forced expiratory volume in one second) of COPD patient 1 is measured according to standard methods after treatment with VIP (200µg in 3 ml 0,9% NaCl per day) for 12 weeks (Figure 1a).

PaO_2 (partial pressure of arterial oxygen) of COPD patient 1 is measured according to standard methods after treatment with VIP (200µg in 3 ml 0,9% NaCl per day) for 12 weeks (Figure 1b)

Patient 2:

A patient with severe COPD symptoms inhaled VIP (100 µg in 3 ml NaCl 0,9%) for 15 minutes via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Lung function parameters FEV1 (forced expiratory volume in one second) and PaO_2 (Partial pressure of arterial oxygen) were measured.

FEV1 (forced expiratory volume in one second) of COPD patient 1 is measured according to standard methods after treatment with VIP (200µg in 3 ml 0,9% NaCl per day) for 12 weeks (Figure 2a).

PaO_2 (Partial pressure of arterial oxygen) of COPD patient 1 is measured according to standard methods after treatment with VIP (200µg in 3 ml 0,9% NaCl per day) for 12 weeks (Figure 2b)

Patient 3

A patient with severe COPD inhaled VIP (100 µg in 3 ml NaCl 0,9%) for 15 minutes via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Lung function parameters FEV1 (forced expiratory volume in one second), VC (Vital capacity), TLC (Total lung capacity), RV (Remaining volume), as well as PaO_2 (Partial pressure of arterial oxygen), AaDO2 (Arterial-alveolar oxygen difference), and PaCO2 (Partial pressure of arterial Carbon Dioxide) were measured.

EXAMPLES FOR ARDS

Patient 4:

A patient with severe ARDS accompanied by pneumonia due to mycoplasm infection inhaled VIP (12 X 200 µg in 3 ml NaCl 0,9%) over a period of 24 hours via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Parameters AaDO2 (Arterial-alveolar oxygen difference), the Horowitz Index, mPAP (mean pulmonary artery pressure), PVR (pulmonary vascular resistance), mABP (mean arterial blood pressure) were measured as shown in the figures.

Patient 5:

A patient with severe ARDS accompanied by pneumonia due to pneumococcus infection and sepsis inhaled VIP (12 X 200 µg in 3 ml NaCl 0,9%) over a period of 24 hours via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Parameters AaDO2 (Arterial-alveolar oxygen difference), the Horowitz Index, mPAP (mean pulmonary artery pressure), PVR (pulmonary vascular resistance), mABP (mean arterial blood pressure), and intrapulmonal shuntvolume were measured as shown in the figures.

Patient 6:

A patient with severe ARDS accompanied by pneumonia due to haemophilus infection inhaled VIP (12 X 200 µg in 3 ml NaCl 0,9%) over a period of 24 hours via the MicroDrop Master Jet (MPV, Truma, Germany) using a particle size of 3 µm to provide alveolar deposition of the substance. Parameters AaDO2 (Arterial-alveolar oxygen difference), the Horowitz Index, mPAP (mean pulmonary artery pressure), PVR

(pulmonary vascular resistance), mABP (mean arterial blood pressure) were measured as shown in the figures.